UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: 10/25/2017

SUBJECT: **Fipronil:** Human Health Risk Assessment of a Proposed Feed-Through for Control of Fleas on Field Rodents

PC Code: 129121	DP Barcode: D437507
Decision No. 524108	Registration No.: 72500-EI
Petition No.: NA	Regulatory Action: Section 3, New Use
Risk Assessment Type: Single Chemical, Aggregate	Case No.: 7423
MRID No.: NA	CAS No.: 120068-37-3

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RD requested that HED conduct a human health risk assessment for the proposed new use of the active ingredient (ai), fipronil, as a feed-through bait for control of fleas on Norway rats and prairie dogs. The end-use product related to this action is Rodent Flea Control Bait with Fipronil, 72500-EI.

Note: This memorandum was reviewed by the Exposure Science Advisory Committee (ExpoSAC) on 10/19/2017.

Executive Summary

HED has conducted a human health risk assessment in support of a proposed fipronil product, EPA Reg. No. 72500-EI. The product registrant, Scimetrics Limited Corporation, has submitted a proposal for a new use of fipronil as a feed-through bait for control of fleas on Norway Rats (*Rattus norvegicus*) and prairie dogs of the genus *Cynomys* in parks, golf courses, rangeland, pasture, alfalfa, wheat, oats, barley, fruit tree orchards (dormant season only), non-crop rights-of-way and other non-crop areas. The registrant has also proposed special application for use in military installations, activity and training areas, desert areas, and areas where sand flies and fleas are prevalent. HED expects only occupational handler (those individuals involved in the pesticide application process) exposure from the proposed product. Exposures to fipronil through ingestion of food or drinking water, and/or in residential settings are not anticipated due to the limited use pattern. This memorandum serves as both the human health risk assessment and occupational and residential exposure and risk assessment for the proposed product. No human health risks of concern were identified that would preclude registration of the proposed product.

The most recent human health risk assessment for fipronil was conducted in conjunction with a petition to support and maintain the established rice grain tolerance for imported rice (PP# 8E7480, D360652, D. Drew, 09/22/2009). All aggregate exposures and risks evaluated were not of concern, including: acute aggregate exposure (food + drinking water), short- and intermediate-term aggregate exposure (food + drinking water + residential exposure), and chronic aggregate exposure (food + drinking water). A cancer aggregate risk assessment was not performed since it was determined that long-term consumption of fipronil residues were adequately addressed by the chronic exposure assessment. No new residential uses or food tolerances have been proposed since the 2009 assessment which would impact the previous aggregate risk finding. Further, the currently proposed rodent feed-through bait product has no impact on the aggregate risk assessment finding for fipronil; therefore, an updated aggregate risk assessment is not required.

Fipronil is currently undergoing registration review.[1] The registration review program is intended to ensure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. During registration review, EPA will evaluate any new exposure or hazard data submitted and update the fipronil human health risk assessment in accordance with current risk assessment science policies.

Exposure Profile

Based on the proposed labeling, occupational handlers are the only exposure scenario expected to occur from use of the proposed product. Users are directed to manually scatter ½ cup of product, equivalent to 0.000010 pounds active ingredient (lbs ai), in and around burrows via spoon or cups for all proposed use sites including special application for military use. The proposed military use also includes broadcast application via mechanical spreader in areas less

[1] Fipronil Summary Document Registration Review: Initial Docket June 2011: https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0448-0003

than 10 acres. The feed-through bait should be directed to the same area every other day for 3 to 4 applications. A continuous supply of bait is needed for 6 to 8 days to ensure that all field rodents have an opportunity to feed on bait for at least 5 consecutive days.

Occupational post-application exposures are not expected. Although reentry into previously treated areas are proposed (i.e., 3 to 4 repeated applications are proposed over a 6 to 8-day period), this activity is not expected to result in additional fipronil exposures since there will be no contact with treated foliar surfaces, nor will the worker contact the previously dispersed rodent feed-through bait material.

Residential exposures are not anticipated from the proposed use despite its proposed use in parks since application in non-military sites are limited to in and around ground rodent burrows. Adults and children would not be expected to frequent such areas and are, therefore, unlikely to come into contact with the fipronil feed-through bait. Further, residential handler exposures from the application of the proposed product are not expected. The proposed label requires that handlers wear long-sleeved shirt, long pants, socks, shoes, and waterproof gloves. Therefore, HED has made the assumption that the proposed product is not for homeowner use, and has not conducted a quantitative residential handler assessment.

Dietary exposures from food and drinking water are also not expected for the proposed use since the proposed product is not applied directly to foods which could be consumed, and since the use site is limited either to individual burrows or up to areas no larger than 10 acres and would not be expected to be a significant drinking water exposure source.

Hazard

A summary of the toxicological doses, endpoints, and levels of concern (LOCs) used this assessment are included in Appendix A of this memorandum. The fipronil points of departure (PODs) and uncertainty factors (UFs) were updated to reflect the current hazard database.

Fipronil has been classified by the HED Cancer Peer Review Committee (CPRC) as a Group C - Possible Human Carcinogen based on increases in thyroid follicular cell tumors in both sexes of the rat.

There are currently outstanding toxicity data for fipronil. A generic data call-in (GDCI) was issued which required a comparative thyroid study for fipronil. The GDCI can be referenced in the registration review docket for fipronil.[2] This study is needed because the thyroid is a target in adults and there has not been an assessment of thyroid function in the young. An additional 10x database uncertainty factor (UF_{DB}) is retained due to the lack of a comparative thyroid study. The 10x UF_{DB} applies to all routes of exposure. A rationale describing the need for the comparative thyroid toxicity study can also be found on the registration review docket for fipronil.[3] To date, these data have not been submitted.

[2] https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0448-0045
[3] https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0448-0043

Exposure Assessment

Occupational Handler Risk Assessment: Due to the likelihood for occupational handler exposures from the loading and application of fipronil rodent feed-through bait, HED has conducted an assessment of the proposed use. A quantitative exposure/risk assessment for occupational handler exposures is based on the following scenarios:

- Loading/applying granules via cup;
- Loading/applying granules via spoon:
- Mixing/loading granular for application via mechanical spreader; and
- Applying granular product via mechanical spreader.

Occupational Handler Exposure Data and Assumptions: A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: The proposed application rate, 0.000010 lb ai product in and around burrows, was used to conduct the occupational handler assessment.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); and the Agricultural Handler Exposure Task Force (AHETF) database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[4]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[5].

Area Treated or Amount Handled: HED assumes that an occupational handler could treat 50 burrows per work day by cup or spoon. For the proposed military use, an area of 40 acres is assumed to be treated by mechanical spreader at a rate of 50 burrows per acre treated (assuming 4, 10 acre areas are treated). The acreage estimate is based on the recommendation for groundboom turf application to golf courses based on guidance in ExpoSAC Policy 9.1, *Standard Values for Daily Area Treated Values for Agricultural Applications*.

Exposure Duration: Based on the proposed use pattern, HED assumes that occupational handlers of the rodent feed-through bait product could be exposed over a short-term (1 to 30 days) exposure duration. For fipronil, the short- and intermediate-term (30 days to 6 months) dermal and inhalation points of departure are the same; therefore, estimates for short-term durations are protective of intermediate-term exposure durations.

[4] Available: https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[5] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Mitigation/Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated based on the proposed level of attire, long-sleeved shirt, long pants, socks, shoes, and waterproof gloves.

Body Weight: The standard body weight for the general population (80 kg) was used for the occupational handler exposure scenarios covered in this risk assessment since the endpoints selected were not developmental and/or fetal effects.

Absorption: A dermal absorption factor of 1% was used for the exposure assessment based on a dermal absorption study in rats (MRID 44262816). Since no inhalation absorption data are available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations: The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix B of this memorandum.

Combining Exposures/Risk Estimates: Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined Dermal + Inhalation Dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates: The estimated occupational handler risks are summarized in Appendix C of this memorandum. Occupational handler combined dermal and inhalation risks are not of concern (i.e., all MOEs are > the LOC of 1,000).

Conclusion

No human health risks of concern were identified that would preclude registration of the proposed product. Further, the currently proposed rodent feed-through bait product does not impact the 2009 aggregate risk assessment finding for fipronil.

The GDCI for the comparative thyroid toxicity study is outstanding; therefore, an additional 10x UF_{DB} safety factor has been retained for all routes of exposure. If a comparative thyroid toxicity study is submitted and found to be acceptable, the additional safety factor may be removed. During registration review, EPA will evaluate these and any other new exposure or hazard data submitted and update the fipronil human health risk assessment in accordance with current risk assessment science policies.

Appendix A: Fipronil Hazard for Assessment of the Proposed Rodent Feed-Through Bait Use

Table A. 1. Summary of Toxicological Doses and Endpoints for Fipronil for Use in Occupational Human Health Risk Assessment

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) & Intermediate-Term (1– 6 months)	$BMDL_5$ = 0.34 mg/kg/day[1] DAF = 1%	UF_A= 10x UF_H=10x UF_{DB}=10x	LOC =1000	Developmental neurotoxicity study – rat MRID 44039002 Developmental LOAEL = 0.9 mg/kg/day based on decreased pup body weight
Inhalation Short-Term (1-30 days) & Intermediate-Term (1-6 months)	$BMDL_5$ = 0.34 mg/kg/day[1]	UF_A=10x UF_H=10x UF_{DB}=10x	LOC = 1000	Developmental neurotoxicity study – rat MRID 44039002 Developmental LOAEL = 0.9 mg/kg/day based on decreased pup body weight

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). LOC = level of concern. DAF = dermal absorption factor. $BMDL_5$ = Lower bound of the 95% confidence interval of the benchmark dose for a 5% decrease in pup body weight.

[1]Benchmark dose analysis of the pup body weight effects in the developmental neurotoxicity study was conducted by the registrant and reviewed by HED (D436085 Wray 2016)

Appendix B: Summary of Occupational Non-Cancer Algorithms

Occupational Non-Cancer Handler Algorithms

Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

where:

E	=	exposure (mg ai/day),
UE	=	unit exposure (µg ai/lb ai),
AR	=	maximum application rate according to proposed label (lb ai A or lb ai/gal), and
A	=	area treated or amount handled (e.g., A/day, gal/day).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

where:

ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day),
E	=	exposure (mg ai/day),
AF	=	absorption factor (dermal and/or inhalation), and
BW	=	body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a Margin of Exposure (MOE), which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal and inhalation dose received by occupational handlers are compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational handlers for each exposure route. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:

MOE	=	margin of exposure: value used by HED to represent risk estimates (unitless),
POD	=	point of departure (mg/kg/day), and
ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day).

Appendix C: Summary of Estimated Occupational Handler Exposures and Risks

Table C.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Proposed Rodent Feed Through Bait Use of Fipronil

Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Level of PPE or Engineering control	Level of PPE or Engineering control			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Loader/Applicator											
Loading/Applying via Cup	Rodent Burrows	1,000	112 (SL/No Gloves)	12.5 (No Respirator)	0.000010 lb ai/burrow	50 Burrows	$7.0x10^{-9}$	$4.9x10^{7}$	$7.8x10^{-8}$	$4.4x10^{6}$	$4.0x10^{6}$
Loading/Applying via Spoon			4,170 (SL/No Gloves)	121 (No Respirator)			$2.6x10^{-7}$	$1.3x10^{6}$	$7.6x10^{-7}$	$4.5x10^{5}$	$3.3x10^{5}$
Mixer/Loader											
Mixing/Loading for Application via Mechanical Spreader	Rodent Burrows	1,000	8.4 (SL/No Gloves)	1.7 (No Respirator)	0.00050 lb ai/A	40 Acres	$2.1x10^{-8}$	$1.6x10^{7}$	$4.3x10^{-7}$	$8.0x10^{5}$	$7.6x10^{5}$
Applicator											
Application via Mechanical Spreader	Rodent Burrows	1,000	9.9 (SL/No Gloves)	1.2 (No Respirator)	0.00050 lb ai/A	40 Acres	$2.5x10^{-8}$	$1.4x10^{7}$	$3.0x10^{-7}$	$1.1x10^{6}$	$1.0x10^{6}$

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Single Layer (SL), no gloves, and no respirator.
2 Based on proposed label (Reg. No. 72500-EI). 0.000010 lb ai/burrow or 0.0005 lb ai/acre (assuming 50 burrows per acre).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (%) ÷ BW (kg).
5 Dermal MOE = Dermal NOAEL (0.34 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or lb ai/burrow) × Area Treated or Amount Handled (A or burrow) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (0.34 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (mg/kg/day) ÷ Dermal Dose + Inhalation Dose **OR** Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).